

Growth Hormone

Introduction:

- Growth Hormone (GH) is also called somatotrophic hormone or somatotropin.
- It is the primary hormone responsible for regulating overall body growth (somato means "body").
- It is secreted by somatotropes of anterior pituitary gland.

Mechanism of Action:

- It is a protein hormone consisting of a single peptide chain of 191 amino acids.
- It is easily transported in blood plasma.
- However, it is not able to pass through the lipid bilayers of target cells. Instead it binds to a specific receptor located on the outer surface of cell membrane.
- It acts through "Tyrosine Kinase Receptor".

Physiological Effects:

I- Effect on Growth:

- It causes growth of almost all tissues of the body that are capable of growing.
- It stimulates growth of both skeleton & soft tissues.
- It promotes increase in size (Hypertrophy) & number (Hyperplasia) of cells.
- GH increases the size of cells through favoring protein synthesis (by stimulating almost all aspects of protein synthesis, while simultaneously inhibiting protein degradation).
- GH increases the number of cells by stimulating cell division and by preventing apoptosis (programmed cell death).

a) Effect on Skeleton (Bone & Cartilage):

- Increases bone growth both in length (linear) & in thickness.
- This effect is indirect mediated through *somatomedins*.
- Somatomedins acts on bone & cartilage to promote their growth by:
 - Proliferation of epiphyseal cartilage.
 - Deposition of chondroitin sulfate at epiphyseal plate.
 - Increases uptake of sulfur.
 - Increases Ca^{+2} & PO_4^{-3} in bones.
 - Increases collagen synthesis.
 - Increases osteoblastic activity.

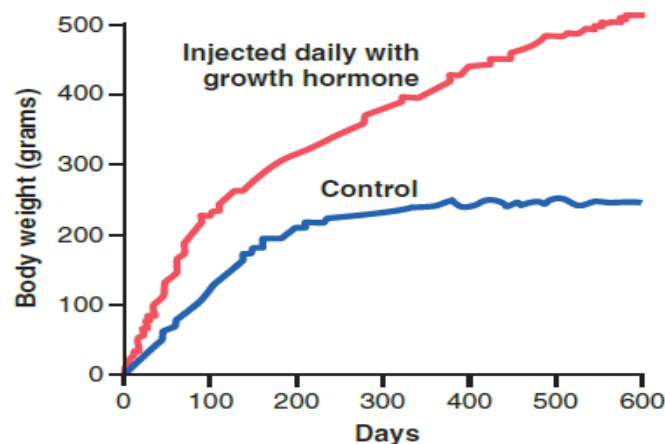
Somatomedins:

- They are proteins synthesized in the liver.
- Somatomedin (or sulphation factor) is the original name.

- Now, these peptide mediators are preferentially called **Insulin-like Growth Factors (IGFs)** because they are structurally and functionally similar to insulin.
- IGFs exert their effects by binding with specific receptor on the target cell "Tyrosine Kinase Receptor".
- There are 2 types; IGF-I & IGF-II.
- The most important one is somatomedin C which is also called IGF-I
- GH acts through somatomedin C = IGF-I
- IGF-I synthesis is stimulated by GH and mediates most of this hormone's growth-promoting actions.

b) Effect on Soft Tissues:

- Generally, GH increases organ size & function.
- Increases muscle mass (= lean body mass).
- This effect is mediated through:
 - Increases amino acid uptake.
 - Increases protein synthesis.
 - Increased DNA, RNA synthesis.
 - Increased cell size and number.



Comparison of weight gain of a rat injected daily with GH with that of normal control.

II- Effect on Metabolism:

- This effect is direct.
- GH binds directly to its target organs, namely:
 - Liver.
 - Adipose tissue.
 - Skeletal muscles.

a) Effect on Protein metabolism:

- GH increases total body protein.

- It has an *anabolic* effect.
- The role of GH on protein metabolism include:
 - Increases amino acid uptake (= enhancement of amino acid transport through the cell membrane).
 - Stimulation of protein synthesis.
 - Increases RNA synthesis.
 - Inhibits protein catabolism (= protein sparing effect).
 - Produces +ve nitrogen balance.

b) Effect on Carbohydrate metabolism:

- GH increases blood glucose level (= Hyperglycemia) & prevents its utilization for energy production.
- It has a *diabetogenic* effect.
- The role of GH on carbohydrate metabolism include:
 - Increases hepatic glucose output (stimulate glycogenolysis & gluconeogenesis).
 - Decreases glucose uptake & utilization by adipose tissue & muscles (= anti-insulin effect).
 - Causes compensatory increase in insulin secretion → insulin resistance.

c) Effect on Lipid metabolism:

- GH enhances Fatty Acids (FA) utilization for energy production.
- It has a *lipolytic* effect.
- The role of GH on lipid metabolism include:
 - Increases mobilization of FA from adipose tissue (= stimulation of lipolysis), through activation of hormone sensitive lipase → fatty liver.
 - Stimulation FA oxidation → production of ketone bodies (Ketogenesis).

d) Effect on Electrolytes:

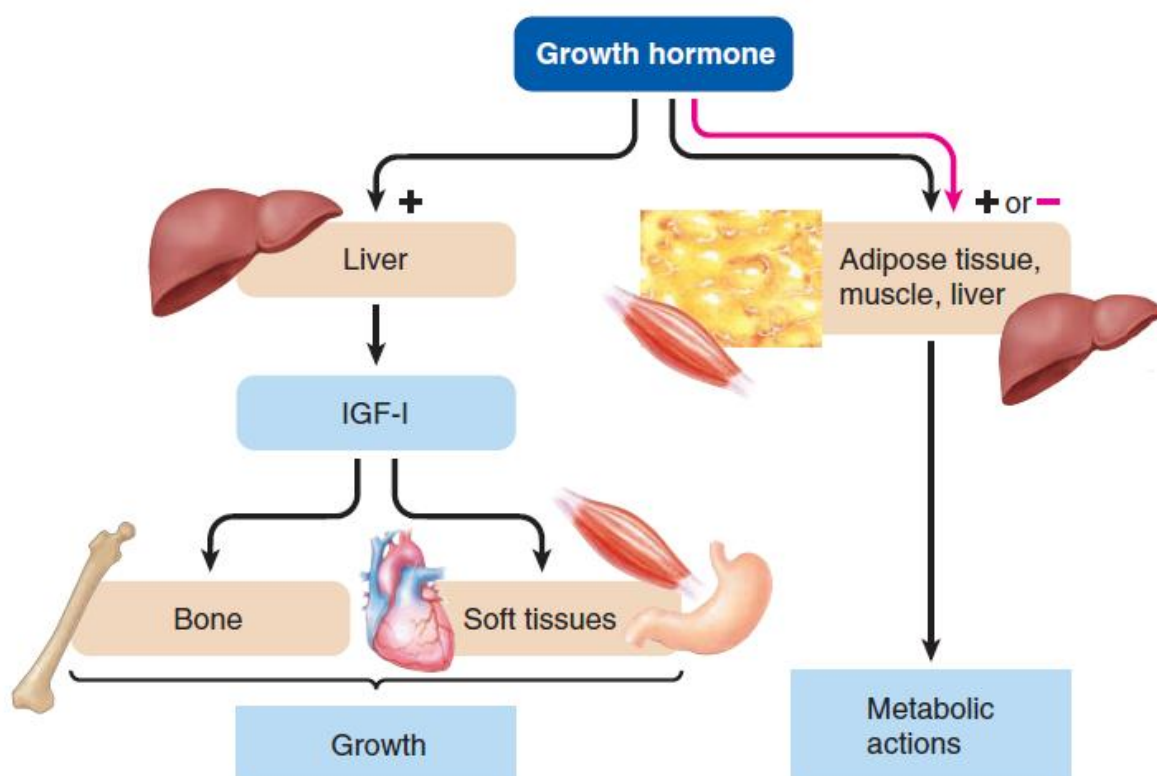
The role of GH on electrolytes includes:

- Increases the intestinal absorption of Ca^{++} (by stimulating vitamin D production).
- Elevates plasma PO_4^{-3} level.
- Reduces Na^+ and K^+ excretion by an action independent of the adrenal glands, probably because these electrolytes are diverted from the kidneys to the growing tissues.

☺ **N.B:**

GH is Anabolic, Lipolytic, Ketogenic & Diabetogenic

- GH ability to promote fat utilization, together with its protein anabolic effect, causes an increase in lean body mass.



Functions of GH secretion

Regulation of Secretion:

The release of GH is under control of:

- I- Hypothalamic hormones.
- II- Feedback loop.
- III- Diurnal rhythm.
- IV- Other factors.

I- Hypothalamic Hormones:

- Two antagonistic regulatory hormones from the hypothalamus are involved in controlling GH secretion:
 - a) **Growth Hormone Releasing Hormone (GHRH)**, which is stimulatory & dominant.
 - b) **Growth Hormone Inhibiting Hormone (GHIH, or somatostatin)**, which is inhibitory.
- The hypothalamic GHRH & GHIH are secreted by nerve endings in the median eminence of the hypothalamus.
- Then they will be transported from there to the anterior pituitary gland in the hypothalamic – hypophyseal portal blood.
- Both GHRH and somatostatin act on the anterior pituitary somatotropes by binding with G-protein coupled receptors linked to the cAMP second-messenger pathway.

- GHRH increasing the cAMP, while somatostatin decreasing cAMP.

II- Feedback Loop:

- 1) GH stimulates IGF-I secretion by the liver, and IGF-I in turn is the primary inhibitor of GH secretion by the anterior pituitary as follows:
 - a) IGF-I directly inhibits the somatotropes in the anterior pituitary.
 - b) IGF-I inhibits GHRH-secreting cells and stimulates the somatostatin-secreting cells in the hypothalamus.
- 2) GH itself inhibits hypothalamic GHRH secretion & stimulates somatostatin release.

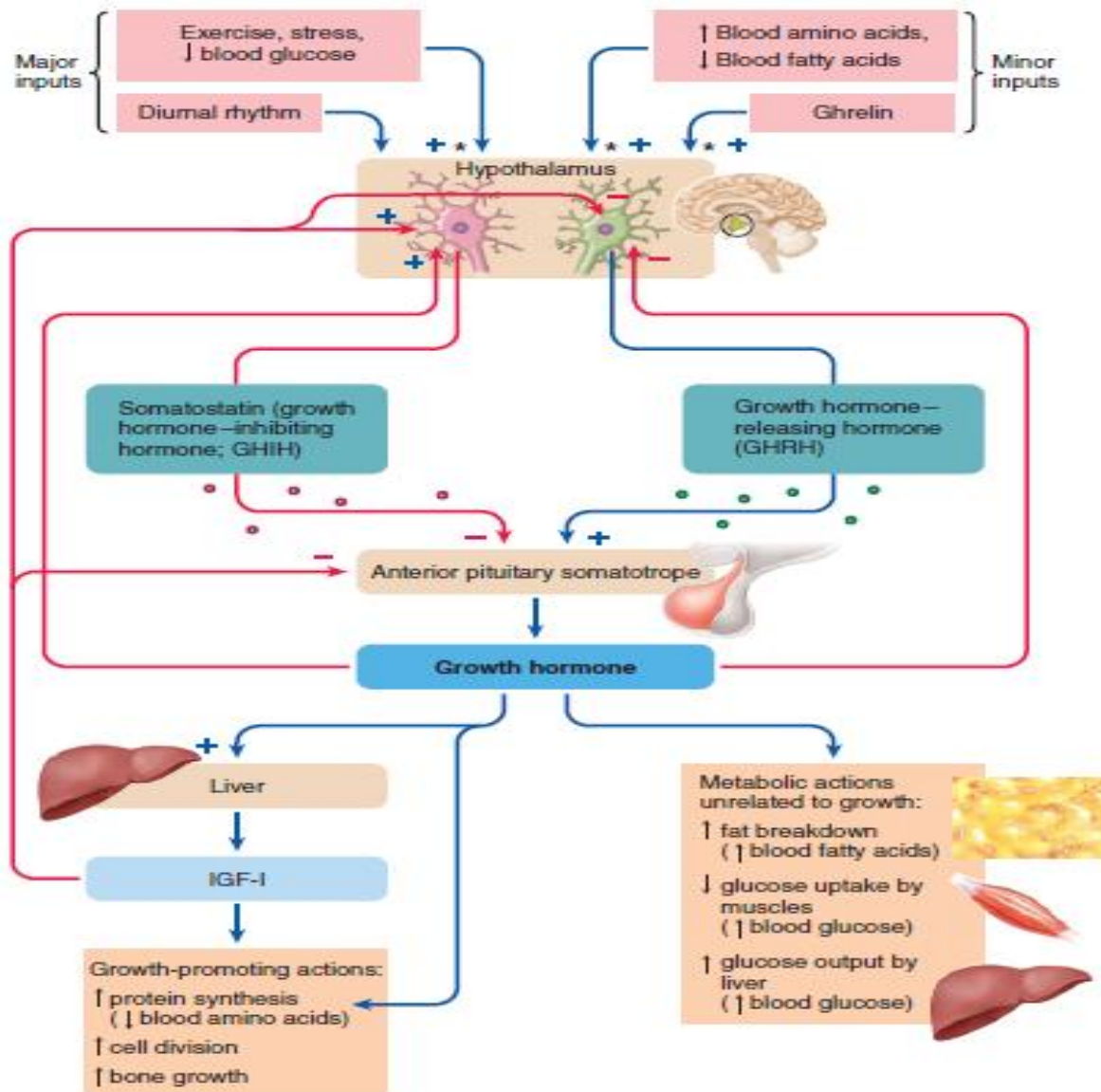
III- Diurnal Rhythm:

- GH is secreted in a pulsatile pattern, increasing & decreasing.
- Most of the day, growth hormone levels tend to be low and constant.
- After the onset (about an hour) of deep sleep, GH secretion increases up to five times the daytime value.
- It rapidly drops over the next several hours.

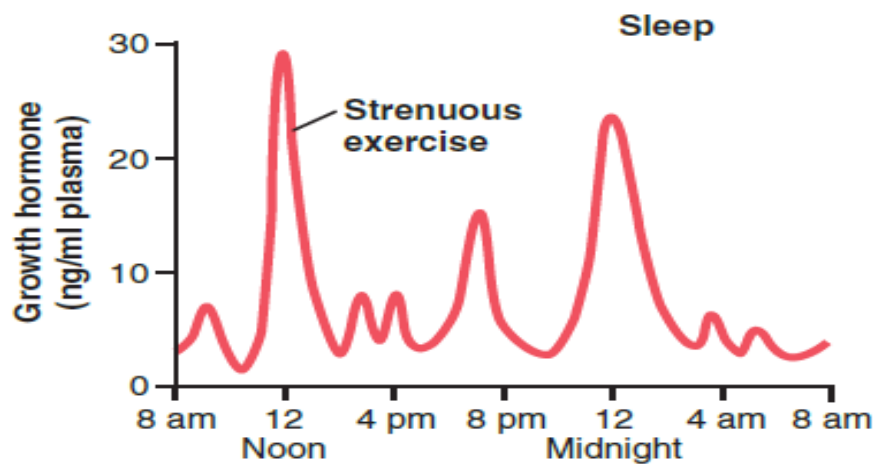
IV- Other Factors:

Superimposed on this diurnal fluctuation in GH secretion are further bursts in secretion that occur in response to:

- a) Deficiency of energy substrates:
 - Lowered blood glucose level (= Hypoglycemia), the most potent factor.
 - Decreased blood FA level.
 - Fasting.
 - Starvation.
- b) Stressful stimuli:
 - Exercise.
 - Excitement.
 - Trauma.
- c) Rise in blood amino acids level:
 - After high protein meal (GH promotes the use of these amino acids for protein synthesis).
- d) Other hormones:
 - Thyroid hormones.
 - Sex hormones (androgens & estrogens).



Control of GH secretion



Variations in GH secretion throughout the day



Blood levels of GH & age:

- For many years it was believed that GH was secreted primarily during the period of growth but then disappeared from the blood at adolescence. This has proved to be untrue.
- After adolescence, GH secretion decreases slowly with aging.
- The smaller amount of GH secreted in adult is needed to maintain the metabolic functions.

	ng/ml
5 to 20 years	6
20 to 40 years	3
40 to 70 years	1.6

Disturbances of GH Secretion:

1) Hyper-secretion of GH:

- Cause:
 - Tumor of the GH-producing cells of the anterior pituitary (mainly).
 - Hypothalamic tumor secreting GHRH (rare).
- Manifestations:
 - Depending on the age of the individual when the abnormal secretion begins.
 - Clinically presented as: Gigantism or Acromegaly.

	Gigantism	Acromegaly
Pathology	<ul style="list-style-type: none"> - Increased secretion of GH before puberty - Before closure of epiphyseal plates 	<ul style="list-style-type: none"> - Increased secretion of GH after puberty - After closure of epiphyseal plates
Cause	Tumor of the GH-producing cells of the anterior pituitary	
	I- <u>Effect on Growth</u>	
	a) <u>Skeleton (Bones & Cartilage) :</u>	
	<ul style="list-style-type: none"> • Symmetrical enlargement of the body (= no distortion of body proportions) • Over growth of long bones 	<ul style="list-style-type: none"> • Asymmetrical enlargement of the body • Over growth of acral (terminal) parts of the skeleton • Acro = extremity, Megaly = large

Clinical Picture

- | | |
|--|---|
| <ul style="list-style-type: none"> Hight increases above 2 meters | <ul style="list-style-type: none"> No increase in hight Bones become thicker Over growth of small bones of hands, feet & cancellus membranous bones Fingers are broad & sausage-like (= Spade-like hand) Large skull (= Box-shaped) Proinent supra-orbital ridges Large protruded mandible (= Prognathism), with wide spaced teeth Enlargement of vertebrae → deformities & kyphosis Osteoarthritis & joint pains Increased cartilagenous growth → enlargement of nose & ears |
|--|---|

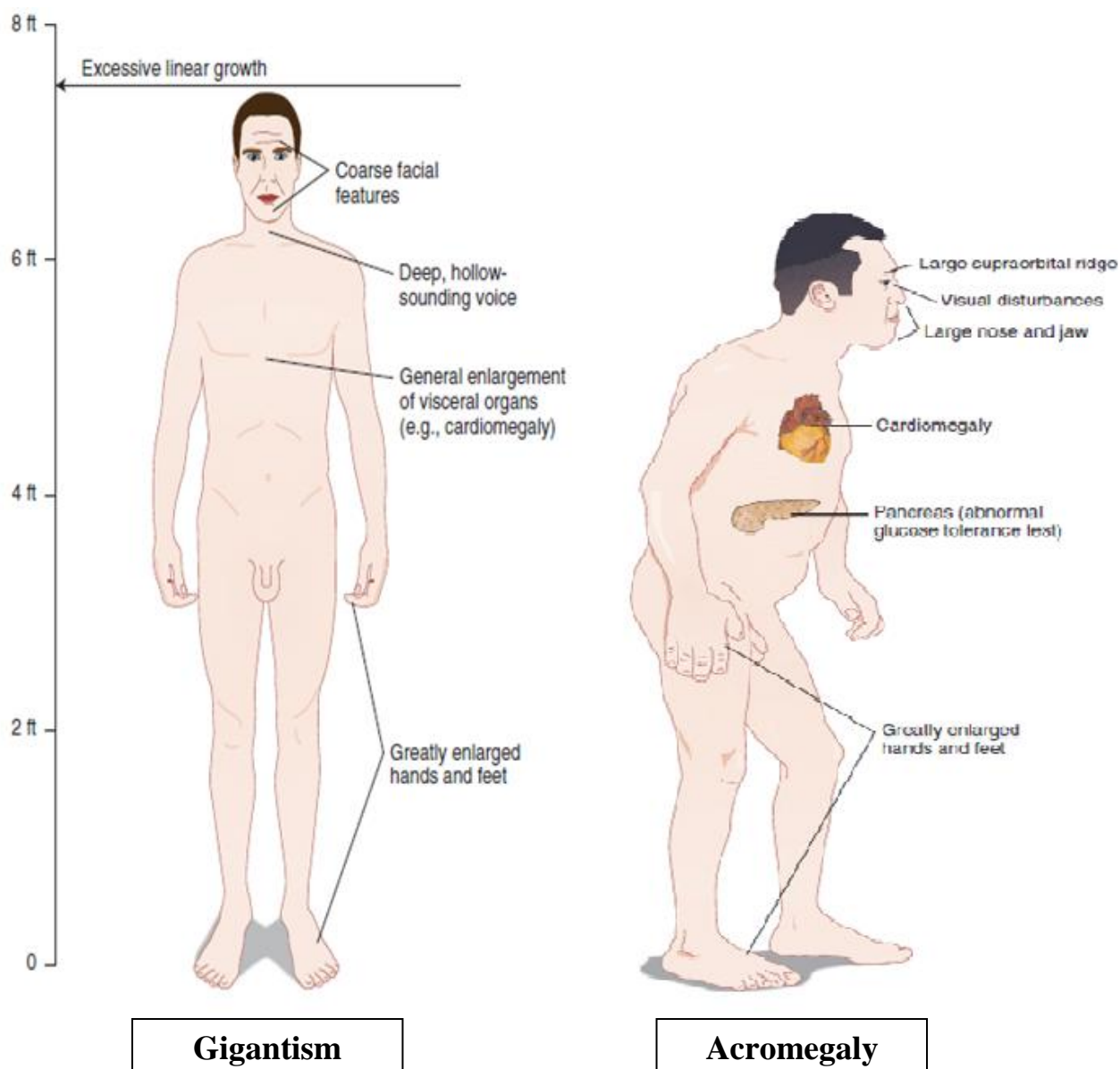
b) Soft Tissues:

- | | |
|---|---|
| <ul style="list-style-type: none"> Enlargement of internal organs (hepatomegaly, splenomegaly, cardiomegaly) Increased muscular strenth (initially) | <ul style="list-style-type: none"> Over growth of connective tissues & skin (glands & hairs) Facial features are coare (= Ape-like) Thick lips & large tongue Thickened, wrinkeled skin (due to over groth of connective tissue) with excessive sweating & sebaceous secretion Over growth of soft tissues of scalp (= Bull dog scalp) Over growth of body hair Hypertrophy of larynx → Deep & husky voice |
|---|---|

II- Endocrinal Disturbances

- | | |
|---|---|
| <ul style="list-style-type: none"> Increased blood glucose level (Hyperglycemia, Diabetes Mellitus) due to anti-insulin effect | <ul style="list-style-type: none"> Gonadal atrophy (= Hypogonadism) leading to: (⊖?) <ul style="list-style-type: none"> ➤ In ♀ → Amenorrhea (stopage of menstruation) ➤ In ♂ → Impotance (no erection) Gynecomastia (= enlarged breast) & Galactorrhea (= increased milk secretion) (⊖?) |
|---|---|

	III-Other Manifestations	
		<ul style="list-style-type: none"> • Hypertension (⊕?) • Peripheral nerve disorders (⊕?) • Visual disturbances (⊕?)
Diagnosis	1. <u>Clinical Picture:</u> See before	
	2. <u>Investigations:</u> <ol style="list-style-type: none"> Hormonal assay (GH level) Radiological examinaions (CAT scan & MRI) 	
Treatment	<ol style="list-style-type: none"> Surgical Removal Hormonal replacement therapy 	



2) Hypo-secretion of GH:

- In most cases, GH deficiency occurs before puberty.
- Clinically presented as: Pituitary Dwarfism or Pituitary Infantilism

➤ **Pituitary Dwarfism**

Pathology:

- It is due to deficiency of GH before puberty.

Cause:

1. Hypothalamic disorder:
 - Absence of GHRH.
2. Pituitary disorder:
 - Absence of GH (inherent deficiency).
 - Secretion of inactive GH.
 - Organic lesion or surgical removal of pituitary.
3. Lack of somatomedins:
 - The liver is unable to secrete somatomedins IGF-I.
4. End organ resistance:
 - Due to receptor defect (= Laron dwarfism).

Clinical Picture:

- a) Effect on growth:
 - Symmetrical growth retardation both in *skeleton & soft tissues*.
 - Stunted growth all over the body, so the proportions are that of a child.
 - Height: 100 – 120 cm (Short stature = Dwarf).
- b) Normal mentality.
- c) Normal sexual development.

➤ **Pituitary Infantilism**

Pathology:

- It is due to deficiency of GH & gonadotropins (both before puberty).

Clinical Picture:

Dwarfism & Hypogonadism

- a) Effect on growth:
 - As pituitary dwarfism (see before).
- b) Normal mentality.
- c) Sexual retardation (= Hypogonadism):
 - Secondary sex organs remain infantile.
 - The sexual characters do not appear.



The effect of abnormalities in GH secretion on growth

☺ Deficiency of GH after puberty:

- GH deficiency in adulthood after growth is already complete produces relatively few symptoms, including:
 - Reduced skeletal muscle mass & strength (because of less muscle protein).
 - Poor exercise performance.
 - Decreased bone density (less osteoblast activity).
 - Hypoglycemia.
 - Progeria (= rapid & premature aging).

Physiology of Growth

Introduction:

- Growth is a complex phenomenon characteristic of living organism.
- It is accompanied by orderly sequence of maturational changes.
- Growth requires:

- Net synthesis of proteins
- Lengthening of the long bones (the bones of the extremities).
- Increases in the size and number of cells in the soft tissues.
- Weight gain alone is not synonymous with growth because weight gain may occur from retaining excess water or storing fat without true structural growth of tissues.
- Although, growth hormone is absolutely essential for growth, it is not wholly responsible for determining the rate and final magnitude of growth in a given individual.

Factors Influencing Growth:

- 1) Genetic Factors
- 2) Adequate Diet:
 - This is the most important extrinsic factor affecting growth.
 - The diet must contains:
 - Sufficient amount of proteins with essential amino acids.
 - Essential vitamins & minerals.
 - Adequate calories, so that ingested proteins is not burned for energy production.
- 3) Freedom from chronic diseases and stressful conditions.
- 4) Hormonal Factors:
 - Normal hormonal levels are essential for growth.
 - The hormones required for growth include:
 - Growth hormone (the most important).
 - Thyroid hormones.
 - Insulin hormone.
 - Sex hormones.
 - Glucocorticoids.

Hormonal Control of Growth:

1. Growth Hormone:
 - Peak action:
 - GH is highest during *adolescence*, the period of most rapid growth.
 - The importance of GH in human growth is from time of birth till 16 years old.
 - Net effect:
 - Stimulate replication (mitosis) of most cells.
 - Promote bone growth & lengthening (indirect through IGF-I).
 - Stimulate protein synthesis in most tissues (direct) → Hypertrophy.
2. Thyroid Hormones:
 - Peak action:

- **Thyroid Hormones (TH)** are important for CNS development during *intrauterine life* & *first few months after birth*.
- The importance of TH in human growth is in the first 4 years of life, then decreasing effect till the age of 20.
- Net effect:
 - Potentiating the actions of IGF-I.
 - Stimulate the secretion of GH.
 - Needed for normal function (= Permissive effect).
 - Promote bone growth & lengthening (particularly long bones).
 - Stimulate protein synthesis (anabolic effect).

3. Insulin Hormone:

- Peak action:
 - Insulin exerts some growth promoting effect *during childhood*.
 - An insulin hormone is highly important during intrauterine life.
- Net effect:
 - Promote cell differentiation & mitosis during intrauterine life.
 - Stimulate the secretion of IGF-I.
 - It can bind & activate IGF-receptors.
 - Stimulate protein synthesis (anabolic effect).

4. Sex Hormones:

- Peak action:
 - They are responsible for pubertal growth spurt.
- Net effect:
 - Powerful stimulant for protein synthesis (anabolic effect) in many organs.
 - Stimulate the secretion of GH & IGF-I.
 - Stimulate linear bone growth, at the same time, *promote closure of epiphyseal plates* (this dual effect explains the pattern seen in adolescence; rapid lengthening of bones followed by complete cessation of growth for life).



Anabolic Steroids:

- They are testosterone like agents, used by athletes to increase their muscle mass & strength.

5. Glucocorticoids:

- These are hormones secreted from adrenal cortex.
- The most known hormone is cortisol.
- They inhibit growth, if administrated in a high dose during growth periods of life.
- Mechanism:

- Inhibit the secretion of GH.
- Inhibit protein synthesis.
- Stimulate protein degradation (catabolic effect).

Growth Periods:

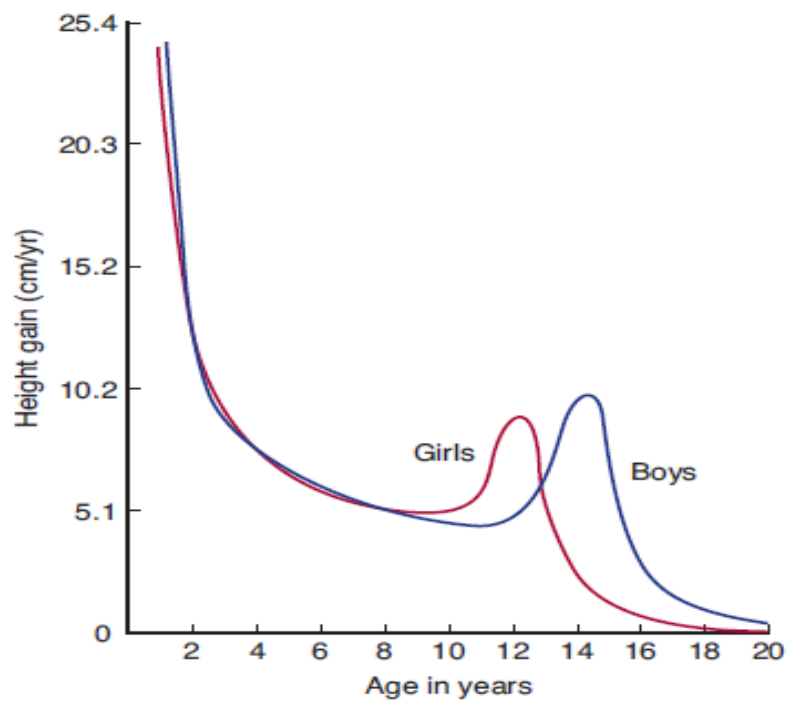
- The rate of growth is not continuous.
- Also, the factors responsible for promoting growth are not the same throughout the growth period.
- Growth periods are divided into:

I- Intra-uterine:

- Hormonal control:
 - Placental hormones (mainly).
 - Insulin & IGF-II (major role).
 - Thyroid hormones (especially for CNS development).
 - GH has **no role** at all during this period.

II- After Birth:

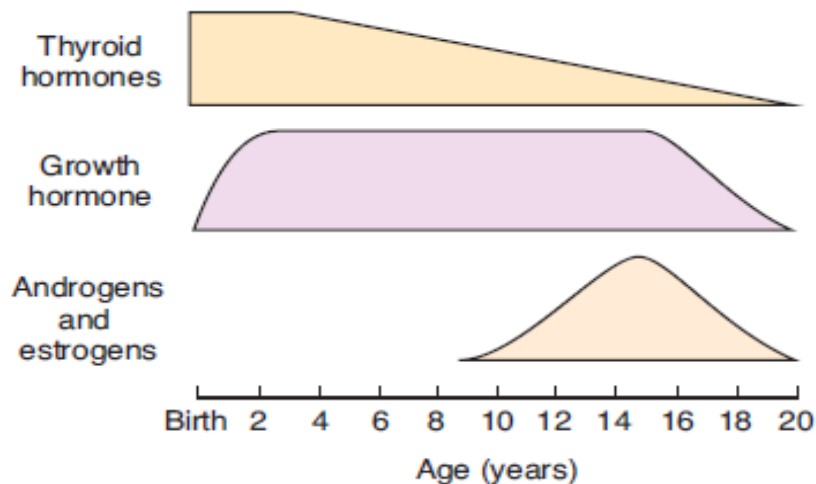
- Children display two periods of rapid growth:
 - a) Post-natal (= neonatal) growth spurt:
 - During the first 2 years of life.
 - The growth is markedly accelerated.
 - Hormonal control (Thyroid hormones & GH).
 - b) Pubertal growth spurt:
 - During adolescence.
 - At puberty, a marked acceleration in linear growth takes place because the long bones lengthen.
 - Puberty begins at about age 11 in girls and 13 in boys and lasts for several years in both sexes.
 - Hormonal control (sex hormones & GH).



Rate of growth in boys and girls from birth to age 20

Intra-uterine life	After Birth		
	Post-natal (Growth Spurt)	In between	Pubertal (Growth Spurt)
• Placental Hormones	• Thyroid hormones	• Growth hormone	• Sex hormones
• Insulin Hormone	• Growth hormone		• Growth hormone
• IGF-II			
• Thyroid hormones			

Hormonal control of growth



Relative importance of hormones in human growth at various ages

Short Individuals

Introduction:

- The terms "dwarf" (= little person) is used to describe a person of short stature.
- Dwarfism, also known as short stature, occurs when an organism is extremely small.
- In humans, it is defined as an adult height of less than 4 feet 10 inches (58 in; 147 cm), regardless of sex, although some individuals with dwarfism are slightly taller.

Types of Dwarfism:

I- Proportionate:

- It is a form of simple short stature, without any deformities.
- Both limbs & trunk are small.

II- Disproportionate:

- Characterized by either short limbs or a short trunk.

Causes of Short Stature:

1) Familial:

- Runs in families due to hereditary causes.

2) Genetic:

- Due to gene defect or mutation.

3) Nutritional:

- Including:
 - Malnutrition (especially low protein intake).
 - Malabsorption.
 - Metabolic disorders.

4) Environmental stress:

- Chronic abuse and neglect can also cause dwarfism in children, independent of malnutrition.

5) Chronic diseases:

- Including:
 - Cardiac.
 - Pulmonary.
 - Renal.
 - Immunological diseases.
 - Cancer.

6) Skeletal problems:

- Including:
 - Bone diseases.
 - Cartilage diseases.

7) Endocrinal diseases:

A) Hypothalamic:

- Decreased production of GHRH.

B) Pituitary:

➤ Pituitary Dwarfism:

- It is due to defect in GH only.
- Causes: see before.

➤ Pituitary Infantilism:

- It is due to defect in GH & gonadotropins.

➤ Pan-hypopituitarism:

- It is due to defect in all anterior pituitary hormones.

C) Thyroid:

- Decreased production of thyroid hormones early in life.
- Hypothyroidism in infants termed "cretinism".

D) Adrenal:

- Excessive production of glucocorticoids hormones "Cushing's Syndrome".
- Cortisol therapy.

E) Pancreatic:

- Deficient insulin hormone as in type-1 diabetes mellitus.

F) Gonadal:

➤ Precocious Puberty:

- Causing early closure of bone epiphyses.

8) Unknown cause:

- In many cases there is no known cause.
- It is termed "constitutional delayed growth".